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Vutrisiran

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Initial Therapy

Vutrisiran (Amvuttra™) **may be considered medically necessary** for adult individuals when used according to the U.S. Food and Drug Administration (FDA) approved label and **ALL** of the following are met:

1. Individual has a confirmatory diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) by a genetic test; AND
2. Presence of clinical signs and symptoms of polyneuropathy characterized by **ONE** of the following:
   - Baseline polyneuropathy disability (PND) IIIb or lower (see Table 1 in Description section); or
   - Baseline familial amyloid polyneuropathy (FAP) Stage one or two (see Table 1 in the Description section); AND
3. Individual does not have **ANY** of the following:
   - New York Heart Association (NYHA) class III or IV heart failure; or
   - Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.); or
   - Prior liver transplantation; AND
4. Individual will not use Amvuttra™ (vutrisiran) in combination with other transthyretin (TTR) reducing agents (e.g., inotersen, tafamidis meglumine, patisiran, etc.).

Continuation Therapy

Continued use of vutrisiran (Amvuttra™) **may be considered medically necessary** when:

1. Individual continues to meet the initial treatment criteria cited above **AND**
2. There is documentation of disease stability or improvement in symptoms (e.g., decrease in neuropathic pain, improved motor function, quality of life assessment, and/or serum TTR levels).

Vutrisiran (Amvuttra™) **is considered experimental, investigational and/or unproven** in all other situations.

NOTE 1: Authorization approval duration (initial and reauthorization): 12 months.

Policy Guidelines

None.

Description

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant genetic disease with variable penetrance. Transthyretin is a transporter protein that carries thyroxine and retinol (vitamin A) and is primarily synthesized in the liver (95%) but also choroid plexus. The gene for transthyretin is located on chromosome 18. Variance in the transthyretin gene results in the production of misfolded transthyretin protein. More than 120 variants have been described, including single variants, compound heterozygotes, and deletions. The valine-to-methionine substitution at position 30 (V30M) is the most common variant observed worldwide, while valine-to-isoleucine substitution at position 122 (V122I) is the most common variant in the United States (U.S.). The misfolded protein generated as a result of a variant in the transthyretin gene is insoluble and accumulates as amyloid fibrils (i.e., amyloidosis) in multiple organs of the body, such as the liver, nerves, heart, and kidneys causing disruption of organ tissue structure and function.

Historically, hATTR was classified into 2 distinct syndromes—amyloidosis with polyneuropathy (previously known as familial amyloid polyneuropathy or FAP) and amyloidosis with cardiomyopathy (previously known as familial amyloid cardiomyopathy). (1) While hATTR patients may show predominance of polyneuropathy or cardiomyopathy, it is now recognized that most patients' manifest signs and symptoms of both syndromes over the course of their disease and, therefore, the current clinical approach treats FAP and familial amyloid cardiomyopathy as 1 hereditary disease with a spectrum of clinical manifestations. (2) The first symptoms of hATTR amyloidosis typically appear between the mid-20s and the mid-60s, involving multiple tissues and organs and often seem unrelated. Neurologic symptoms include severe sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and autonomic dysfunction resulting in orthostatic hypotension, diarrhea, impotence, and bladder disturbances. (3) While the neurologic symptoms of hATTR are among the most physically disabling, cardiac manifestations are the most predictive of early death. Cardiac manifestations include arrhythmias, conduction disorders, cardiomegaly, and heart failure. If the disease is untreated, the median survival for patients with predominantly neuropathic symptoms is 5 to 15 years, while patients with predominantly cardiomyopathic symptoms have a median survival of 2.5 to 6 years. (4, 5)

The FAP stage system and the polyneuropathy disability score are the 2 most commonly used clinical staging systems used and are summarized in Table 1. Higher scores on each of the staging systems are indicative of greater disease severity.

Table 1. Clinical Staging in Hereditary Transthyretin-Mediated Amyloidosis

FAP Stage	Clinical Description
Stage 0	No symptoms
Stage 1	Unimpaired ambulation
Stage 2	Assistance with ambulation required
Stage 3	Wheelchair-bound or bedridden

PND Score	
Stage 0	No symptoms
Stage I	Sensory disturbances but preserved walking capability
Stage II	Impaired walking capacity but ability to walk with a stick or crutches
Stage IIIA	Walking with the help of 1 stick or crutch
Stage IIIIB	Walking with the help of 2 sticks or crutches
Stage IV	Confined to a wheelchair or bedridden

Adapted from Ando et al. (2013) (3).
FAP: familial amyloid polyneuropathy; PND: polyneuropathy disability.

Diagnosis

Diagnosis of hATTR based on clinical signs and symptoms is difficult because of heterogeneity in clinical manifestations and the nonspecific nature of signs and symptoms that may mimic other conditions. Furthermore, the age of onset and rate of progression are highly variable from patient to patient. (2) As a result, many patients are misdiagnosed or diagnosis is delayed, and patients often see physicians across multiple specialties before receiving an accurate diagnosis. (2)

To confirm the diagnosis, proven amyloid deposition in biopsy specimens and identification of a pathogenic variant in the transthyretin gene are necessary. (6) Amyloid deposition in the biopsied tissues can be confirmed by using Congo red staining and, ideally, immunohistochemical study as well as laser capture tandem mass spectrometry. However, mass spectrometry can only demonstrate a mass difference between wild-type and transthyretin protein variants in serum. It does not specify the site and kind of amino acid substitution in a number of disease-related transthyretin variants; thus, DNA sequencing is usually required. Sequence analysis of the transthyretin gene, the only gene in which mutation is known to cause hATTR, detects more than 99% of pathogenic variants. (6)

There are currently 2 genetic tests programs that offer no-cost, confidential genetic testing and genetic counseling services sponsored by the manufacturers of inotersen and patisiran. These are summarized in Table 2.

Table 2. Characteristics of Genetic Testing Program Offered by Manufacturers in the U.S.

Program	Program Eligibility	Tests Offered	Detail
AlnylamAct™	Patients 18 years and older with a suspected diagnosis or a confirmed family history of hATTR amyloidosis.	Invitae Cardiomyopathy Comprehensive Panel	Testing for ~50 genes associated with inherited cardiomyopathy conditions, including hATTR amyloidosis
		Invitae Comprehensive Neuropathies Panel	Testing for ~70 genes that cause dominant, recessive, and X-linked

			hereditary neuropathies, including hATTR amyloidosis
		Invitae Transthyretin Amyloidosis Test	Single-gene genetic testing for the TTR gene, which is associated with hATTR amyloidosis
The hATTR Compass™ Program	Patients who are 18 years and older and who have a family history of or are experiencing symptoms of hATTR amyloidosis.	hATTR Amyloidosis Test	Single-gene test for TTR
		CardioNext	Up to 85-gene panel targeting patients with cardiomyopathies, including hATTR amyloidosis
		NeuropathySelect	80-gene panel targeting patients with hereditary neuropathies, including hATTR amyloidosis (available at select centers)

Adapted from AlnylamAct™ and The hATTR Compass™ Program (7, 8)
hATTR: hereditary transthyretin-mediated amyloidosis; TTR: transthyretin gene.

Epidemiology

It is estimated that the neuropathy-predominant form of hATTR affects at least 10,000 people worldwide, (9) and roughly 3,000-3,500 people in the U.S. (10) Due to under-diagnosis and a lack of population-based data, these numbers may underestimate the actual prevalence. (11) According to unpublished data from Alnylam, there may be 10,000 to 15,000 individuals with the neuropathy-predominant form of hATTR Academy of managed care pharmacy [AMCP dossier].

The prevalence of the cardiomyopathy form of hATTR is also problematic to estimate. About 50,000 people worldwide may have hATTR amyloidosis. (9, 10) In the U.S. general population, the prevalence of V122I variant (which is the most common variant seen in the U.S.) is 3.4%. (12) However, phenotypic penetrance resulting in overt clinical cardiac disease depends on age and varies widely from 7% to 80%. (13) Higher estimates of clinical prevalence were reported in studies with very small samples of carriers. Characteristics of hATTR in the U.S. by different variants are summarized in Table 3.

Table 3. Characteristics of hATTR in the U.S. by Variants

Variant	Median Age at Symptoms Onset (Year)	Median Age at Diagnosis (Year)	Median Age at Death (Year)
T60A	60.2	64.5	67.6
V30M	64.3	67.8	74.7
V122I	63.7	69.3	72.9
S77Y	55.8	60.1	65.8
Other	53.1	56.7	62.1

Adapted from Swiecicki et al. (2015) (14)
hATTR: hereditary transthyretin-mediated amyloidosis

Treatment

Prior to the approval of patisiran and inotersen in 2018, there was no Food and Drug Administration (FDA) approved treatment available in the U.S. for the treatment of hATTR. Management approaches include the use of pharmacotherapy with tetramer stabilizers (such as diflunisal and tafamidis) and surgery (orthotopic liver transplant).

Diflunisal, a generic nonsteroidal anti-inflammatory drug, is not approved by the FDA for the treatment of hATTR but is available in the U.S. as a generic and is used off-label. Diflunisal has been shown to stabilize transthyretin tetramers in a phase I study (15) and significantly reduce the progression of neurologic impairment and preserve the quality of life in a randomized controlled trial. (16) Although the results of the randomized controlled trial were positive, multiple limitations with long-term use of diflunisal such as gastrointestinal bleeding, worsening of renal insufficiency, and cardiovascular events (e.g., myocardial infarction, stroke) preclude its long-term use. Further, diflunisal does not reverse neurologic or cardiac impairment.

Tafamidis received FDA approval in 2019 for treatment of hATTR patients with cardiomyopathy. (17) Results of the ATTR-ACT trial published in 2018 reported reduction in the risk of all-cause mortality by 30% compared to placebo (29.5% vs. 42.9%; HR=0.70; 95% CI, 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations by 32% (0.48 vs. 0.70 per year; 95% CI, 0.56 to 0.81). (18)

As transthyretin is primarily formed in the liver, orthotopic liver transplantation has been the disease-modifying treatment available to most patients with hATTR. This procedure can remove approximately 95% of the production of variant transthyretin. However, limited organ availability, exclusion of older patients and those with advanced disease, the high costs of transplantation, the risks of lifelong immunosuppression, and reports of disease progression following liver transplantation limits it use. Further, orthotopic liver transplantation is not recommended for patients with cardiac involvement due to the observed post-transplant progression of cardiomyopathy; making a large proportion of patients in the U.S. who will develop cardiomyopathy ineligible for transplantation. (19) As such, the procedure is not commonly performed in the U.S.

<u>Mechanism of Action</u>

The function of small interfering ribonucleic acid (RNA) is to regulate gene expression, or how much protein will be made from a particular gene. Vutrisiran is a double-stranded siRNA-GaINAc (small interfering RNA *N*-acetylgalactosamine) that interferes with the expression of the transthyretin (TTR) gene, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues. (21)

Regulatory Status
In June 2022, the U.S. Food and Drug Administration (FDA) approved Vutrisiran (Amvuttra™, Alnylam Pharmaceuticals, Cambridge, MA) for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (21)

The recommended dosage of vutrisiran is 25 mg, administered as a subcutaneous injection once every three months by a healthcare professional. (21)

Rationale

This policy was created in October 2022 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 20, 2023. This policy is based in part on the U.S. Food and Drug Administration (FDA) approved clinical indications for vutrisiran (Amvuttra™).

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and the ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR)
Clinical Context and Therapy Purpose

The purpose of patisiran for individuals with polyneuropathy of hATTR is to provide a treatment option that is an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest are individuals with polyneuropathy of hATTR.

Interventions
The therapy being considered is vutrisiran.

Comparators
Management approaches include the use of pharmacotherapy with tetramer stabilizers (such as diflunisal and tafamidis) and surgery (orthotopic liver transplant). Tafamidis is approved in the European Union and several South American and Asian countries but not in the U.S. Orthoptic liver transplantation has also shown to be beneficial but is less frequently used in the U.S.

Outcomes
The general outcomes of interest are related to assessing the impact of disease on sensorimotor, autonomic and cardiovascular manifestations.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Evidence includes one pivotal multicenter, randomized, open labeled trial HELIOS-A (20). The trial randomized 166 adults to vutrisiran or patisiran. Ninety-seven percent of vutrisiran-treated study participants and ninety-three percent of patisiran-treated study participants completed at least 9 months of the assigned treatment. Efficacy assessments were based on a comparison of the vutrisiran arm with an external placebo group in another study (APOLLO; NCT01960348. The APOLLO study was a randomized, double-blind, placebo-controlled trial which randomized 225 study participants with hATTR-PN to patisiran or placebo for 18 months. At 9 months, treatment with vutrisiran resulted in statistically significant treatment difference versus placebo in the mNIS+7 (-17.0 points, p<.001), Norfolk QoL-DN total score (-16.2 points, p<.001), and 10-

meter walk test (0.13 points, p<.001). Vutrisiran was also compared to the patisiran group in the HELIOS-A extension trial for the secondary outcome of mean steady state transthyretin (TTR) reduction from baseline. Vutrisiran was noninferior to patisiran at 18 months (median TTR difference, 5.28%; 95% CI, 1.17 to 9.25; lower limit of CI >-10%).

Common adverse events (AE) occurring in > 10% of study participants were falls, pain extremities, diarrhea, peripheral edema, urinary tract infection (UTI), arthralgia, and dizziness. Arthralgia and pain in extremities occurred more frequently with vutrisiran than APOLLO placebo. Injection-site reactions occurred in 4.1% of study participants on vutrisiran. Serious AEs (SAEs) and severe AEs occurred numerically less frequently with vutrisiran than APOLLO placebo or patisiran (SAEs: 26% vutrisiran, 40% APOLLO placebo, 43% patisiran; severe AEs: 16%, 36% and 38% respectively). Two SAEs (dyslipidemia and UTI) were considered related to vutrisiran. No hepatic, hematologic, or renal safety signals were considered related to vutrisiran. No discontinuations due to AEs were considered related to vutrisiran. No drug-related deaths were identified. No major gaps were identified in the study design and conduct.

Table 4. Summary of Key RCT Characteristics

Study: Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	**Comparator**
Adams et al. (2022) (20); HELIOS-A	Multiple countries	57	2019-2020	Inclusion Criteria: • Adults 18-65 years of age with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), Karnofsky Performance Impairment Status (KPS) ≥ 60%, polyneuropathy disability (PND) ≤IIIb, and Neuropathy Impairment Scale (NIS) 5-130 out of 244 (higher score indicates greater disability) Exclusion Criteria	Vutrisiran q3 months 25 mg subcutaneous injection (N=122)	Placebo arm of APOLLO trial subcutaneous injections (N=77) for the primary endpoint (mNIS+7) and secondary endpoints (Norfolk QoL-DN score, 10-MWT, mBMI and R-ODS) Patisiran 0.3 mg/kg IV q3 weeks for the secondary endpoint (mean steady state transthyretin (TTR)

				• Patients undergoing liver transplantation and those with New York Heart Association (NYHA) class III or IV heart failure Primary endpoint • Change from baseline to month 9 in the modified neuropathy impairment score +7 as compared to the placebo group from the APOLLO study		reduction from baseline

RCT: randomized clinical trial; mNIS+7: modified Neuropathy Impairment Score +7; 10-MWT: 10-meter walk test; mBMI: modified body mass index; R-ODS: Rasch-built Overall Disability Scale score; IV: intravenously.

Table 5. Summary of Key RCT Results

Study	**mNIS+7[a]**	**Norfolk-QOL-DN[a]**	**10-MWT[b]**	**mBMI[c]**
Adams et al. (2022) (20); HELIOS-A	**Change from baseline to 9 months (SEM)**	**Change from baseline to 9 months (SEM)**	**Change from baseline to 9 months (m/sec)**	**Change from baseline to 9 months (kg/m^2)**
Vutrisiran (N=122)	-2.2 (1.4)	-3.3 (1.7)	0 (0.02)	7.6 (7.9)
Placebo[d] (N=77)	14.8 (2.0)	12.9 (2.2)	-0.13 (0..03)	-60.2 (10.1)
Difference in LS Mean Difference (95% CI), p value	-17.0 (-21.8, -12.2); (p<0.001)	-16.2 (-21.7, -10.8); (p<0.001)	0.13 (0.07, 0.19); (p<0.001)	67.8 (43.0, 92.6); (p<0.001)

RCT: randomized clinical trial; mNIS+7: modified Neuropathy Impairment Score +7; 10-MWT: 10-meter walk test; mBMI: modified body mass index; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; m/sec: meters per second; kg/m^2: kilograms per meter squared, CI = confidence interval; LS mean = least squares mean, SEM = standard error of the mean

[a] A lower number indicates less impairment/fewer symptoms

[b] A higher number indicates less disability/less impairment

[c] mBMI: nominal p-value; body mass index (BMI; kg/m2) multiplied by serum albumin (g/L)

[d] External placebo group from another randomized controlled trial (NCT01960348)

The purpose of the study limitations tables (Table 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. A gap in relevance for HELIOS-A trial is related to the duration of the study which is insufficient to ascertain durability and safety. No major gaps were identified in study design and conduct.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Adams et al. (2022) (20); HELIOS-A					1, 2. (9 months follow-up is insufficient to establish long-term benefits and harms)

The study limitations in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a]Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b]Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c]Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d]Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e]Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Summary of Evidence

For individuals who are adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) who receive vutrisiran, the evidence includes 1 pivotal randomized controlled trial (RCT). Relevant outcomes are symptoms, change in disease status, functional outcome, quality of life (QOL), treatment-related morbidity and treatment-related mortality. Data from the HELIOS-A trials demonstrated a statistically significant improvement in neurological function and neuropathy-related QOL with vutrisiran compared to placebo. However, vutrisiran was compared to the placebo arm of the previous APOLLO trial. There is uncertainty regarding long-term benefits and harms for a treatment that is intended to be used lifelong. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0225

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. J Am Coll Cardiol. Dec 01 2015; 66(21):2451-2466. PMID 26610878
2. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. Jun 2017; 23(7 Suppl):S107-S112. PMID 28978215
3. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. Feb 20 2013; 8:31. PMID 23425518
4. Arvanitis M, Chan GG, Jacobson DR, et al. Prevalence of mutant ATTR cardiac amyloidosis in elderly African Americans with heart failure. Amyloid. Dec 2017; 24(4):253-255. PMID 29052438
5. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. Feb 2016; 29 Suppl 1:S3-S13. PMID 26734951
6. Sekijima Y. Familial Transthyretin Amyloidosis. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews((R)). Seattle (WA)1993. PMID 20301373
7. AlnylamAct. Available at: <https://www.invitae.com> (accessed September 20, 2023).
8. hATTR Compass. Available at: <http://www.hattrchangethecourse.com> (accessed September 22, 2023).
9. Kato-Motozaki Y, Ono K, Shima K, et al. Epidemiology of familial amyloid polyneuropathy in Japan: Identification of a novel endemic focus. J Neurol Sci. Jul 15 2008; 270(1-2):133-140. PMID 18410945
10. Plante-Bordeneuve V. Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. J Neurol. Jun 2014; 261(6):1227-1233. PMID 24888313
11. ICER. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value: Final Evidence Report (October 4, 2018). Available at: <https://www.icer.org> (accessed September 20, 2023).
12. Jacobson DR, Alexander AA, Tagoe C, et al. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. Amyloid. 2015; 22(3):171-174. PMID 26123279
13. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med. Jan 01 2015; 372(1):21-29. PMID 25551524

14. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 2015; 22(2):123-131. PMID 26017327
15. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. Amyloid. Dec 2006; 13(4):1236-1249. PMID 17107884
16. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. Dec 25 2013; 310(24):2658-2667. PMID 24368466
17. U.S. FDA approves Vyndaqel and Vyndamax for use in patients with transthyretin amyloid cardiomyopathy, a rare and fatal disease. Available at: <https://www.pfizer.com> (accessed September 20, 2023).
18. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. Sep 13 2018; 379(11):1007-1016. PMID 30145929
19. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. Liver Transpl. Mar 2015; 21(3):282-292. PMID 25482846
20. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. July 23 2022; 1-9. PMID 35875890
21. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Amvuttra™. (Revised 6/2022). Available at: <http://www.accessdata.fda.gov> (accessed September 20, 2023).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/15/2024	Reviewed. No changes.
12/01/2023	Document updated with literature review. The following change was made to coverage: Policy statement for continuation of therapy condensed to “Individual continues to meet the initial treatment criteria above”. No new references added; others updated.
03/01/2023	New medical document. Amvuttra™ (vutrisiran) may be considered medically necessary for adult patients with a confirmatory diagnosis of

	hereditary transthyretin-mediated amyloidosis who meet criteria. Amvuttra™ (vutrisiran) is considered experimental, investigational and/or unproven in all other situations. NOTE 1: Authorization approval duration (initial and reauthorization): 12 months.